REMARKS

Status of the Claims

Claims 1 and 22-28 are pending in the present application. Claims 2-8 and 14-21 are presently canceled. Claims 9-13 were previously canceled. Claim 1 is amended. Claims 22-28 are new. Support for amended claim 1 and new claims 22-28 is found throughout the application as originally filed including, *e.g*, in amended Tables 2, 4, and 6, as described above, and in original claim 3, now canceled. Accordingly, no new matter is added by way of this amendment. Reconsideration is respectfully requested.

Amendments to the Specification

Tables 2, 4, and 6 are amended. Table 2 is amended to specify TAA+2008 and TAA+2025 in lieu of TAA+2007 and TAA+2026, respectively. Table 4 is amended to specify TAA+C2008T in lieu of TAA+C2007T. Table 4 is further amended to add the gene polymorphism TAA+G2025A and a sequence comprising this gene polymorphism. Support for these amendments is inherent throughout the specification as originally filed and as described in the Ikeda Declaration, *enclosed.* An ordinary artisan recognizes that the described C/T and G/A polymorphisms in the 3' untranslated region are necessarily and inherently located at positions 2008 and 2025 from the stop codon in the mu-opioid receptor, rather than 2007 and 2026 bases from the stop codon. Thus, these corrections do not represent new matter.

Support for the new sequence is also inherent in the present application and as described in the Ikeda Declaration. As explained, *e.g.*, on page 25 of the present application, oligonucleotides are contemplated, which have the polymorphism at base 51, *see also* Table 4, in which all of the olignucleotides are of 101 bases with the polymorphism at position 51. Table 2 disclosed the TAA + G2025A polymorphism. One skilled in the art would readily recognize, based on the 67 other corresponding oligonucleotides, that the oligonucleotide containing TAA+G2025 would necessarily be that of new SEQ ID NO: 100. An ordinary artisan, accordingly, inherently recognizes from the present application that the location of the

TAA+G2025A in the mu-opioid receptor and the 50 nucleotides upstream and downstream of the polymorphism.

Table 6 is also amended to change the format of 1.000 from the underlined format to a bold and italicized format at the intersection of the fifth line specifying IVS3+A6151G and the sixth row specifying IVS3+A8449G. Table 6 is further amended to change the value 0.001 at the intersection of the sixth line specifying IVS3 +A8449G and the fifth row specifying IVS3+A6151G to 0.800, and to amend the format of the value at this position from plain text to bold and italicized text.

Support for the Table 6 amendments, which indicate significant D' and r^2 values, are also inherently supported by the present application and described in the Ikeda Declaration. An ordinary artisan repeating the linkage disequilibrium analysis described in the present application, *e.g.*, on pages 27-31, would have determined that the initially reported D' and r^2 values were incorrect because both values, in fact, reach significance. Accordingly, the significance of the amended values is inherently supported. In view of the above, no new matter is added by way of this amendment.

Amendments to the Sequence Listing

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The substitute sequence listing includes new SEQ ID NO: 100. SEQ ID NO: 100 is the sequence identifier for the newly added sequence described above. Based upon the support in the Ikeda Declaration and as described above, the Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is an electronic CRF copy of the Substitute Sequence Listing. The electronic CRF copy of the Substitute Sequence Listing is identical to the paper copy, except that it lacks formatting. Accordingly, no new matter is added by way of this amendment.

Request for Consideration of Amended Claims

Applicants note that the claims, as amended, do not explicitly recite the elected haplotype, *i.e.*, AGAC of Table 8. However, IVS3+A6151G of SEQ ID NO: 28, which is explicitly recited in the claims, is contained within AGAC. Accordingly, since IVS3 + A6151G of SEQ ID NO: 28 is encompassed by amended claim 1 and the elected haplotype, it is believed that the election has constructively been maintained and that the Examiner can continue examination of the claims as amended.

Statement of the Interview

Applicants and Applicants' representative thank the Examiner for extending the courtesy of an interview on September 17, 2009. The substance of the interview is essentially as described in the interview summary of September 25, 2009.

Claim Objections

Claims 1-8 and 14-21 are objected to for including non-elected subject matter, *see* Office Action, page 2. The Examiner states that prior to allowance of any claim, non-elected subject matter that is not rejoined with the elected combination and also allowed will be required to be deleted from the claim, *see* Office Action, page 2. Accordingly, Applicants submit that non-elected subject matter is not presently required to be canceled. Applicants request that at the time allowable subject matter directed to the polymorphism, IVS3+A6151G, encompassed by the elected haplotype, *see* above, the Examiner consider the non-elected subject matter for rejoinder. *See* MPEP § 1893.03(d).

Claims 1 and 14 are objected to for allegedly including a grammatically incorrect phrase. The Examiner states that claim 1 and claim 14 should specify "gene polymorphisms that are in linkage disequilibrium." Claim 14 is canceled. Accordingly, the objection is moot in regard to this claim. Claim 1 is amended as the Examiner recommends. Accordingly, withdrawal of the objection is respectfully requested.

Issues under 35 U.S.C. § 112, Second Paragraph

Claims 5, 6, 18, and 19

Claims 5, 6, 18, and 19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking clarity, *see* Office Action, page 3. Specifically, the Examiner states that the claims unnecessarily reference tables. The Examiner suggests that the claims be amended to describe the polymorphisms and haplotypes by sequence identifiers.

Claims 5, 6, 18, and 19 are canceled. Accordingly, the rejection is moot in regard to these claims.

Claim 1, as amended, describes the sequence identifiers, which correspond to the polymorphism positions described in Table 2. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 7, 8, 20, and 21

Claims 7, 8, 20, and 21 are also rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking clarity, *see* Office Action, pages 3-4. Specifically, the Examiner states that there are no method steps in the claims and that the phrase "using an index, a result" is unclear.

Claims 7, 8, 20, and 21 are canceled. Accordingly, the rejection is moot in regard to these claims. Applicants submit that claim 1, as amended, includes a method step and does not specify the allegedly unclear phrase. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 14

Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly specifying an unclear purpose, *see* Office Action, page 4. Claim 14 is canceled. Accordingly, the rejection is moot.

Issues under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 1-8 and 14-21 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, *see* Office Action, pages 4-6. The Examiner asserts that the claims fail to support a haplotype, which is estimated from gene polymorphisms that are in linkage disequilibrium, to evaluate drug sensitivity or to diagnose an administered dose. In particular, the Examiner states that the present application does not provide limiting structures, as to what nucleotide content of gene polymorphisms, in a particular degree of linkage disequilibrium, are required to estimate the elected haplotype.

Claims 2-8 and 14-21 are canceled. Accordingly, the rejection is moot in regard to these claims.

Although Applicants do not agree that the claims fail to comply with the written description requirement, the claims are amended in an effort to expedite prosecution. As amended, claim 1 is directed to a method of evaluating sensitivity of an individual human subject to a drug, which comprises: linking a gene polymorphism to individual drug sensitivity, the gene polymorphism being selected from the group consisting of: IVS3 + A6151G of SEQ ID NO: 28; IVS3+A8449G of SEQ ID NO: 29, TAA+G886A of SEQ ID NO: 33, TAA+T1360C of SEQ ID NO: 34, TAA+T1371C of SEQ ID NO: 35, TAA+G1670A of SEQ ID NO: 36, TAA+G1709A of SEQ ID NO: 37, TAA+C2008T of SEQ ID NO: 38, TAA+A2109G of SEQ ID NO: 39, TAA+A2274G of SEQ ID NO: 40, TAA+G2287A of SEQ ID NO: 41, TAA+G2395C of SEQ ID NO: 42, TAA+G2458C of SEQ ID NO: 43, TAA+T2482C of SEQ ID NO: 44, TAA+G2497A of SEQ ID NO: 45, TAA+G2656T of SEQ ID NO: 46, TAA+C2714A of SEQ ID NO: 47, TAA+G2820T of SEQ ID NO: 48, TAA+G2907T of SEQ ID NO: 49, TAA+T3423C of SEQ ID NO: 50, TAA+A4026G of SEQ ID NO: 51, TAA+4585(A)n of SEQ ID NO: 52, TAA+A4861C of SEQ ID NO: 53, TAA+A5359G of SEQ ID NO: 54, TAA+A6074C of SEQ ID NO: 55, TAA+T6866G of SEQ ID NO: 56, TAA+C6922G of SEQ ID NO: 57, TAA+7075del(322bp) of SEQ ID NO: 58, TAA+C7427T of SEQ ID NO: 59, TAA+7483del(A) of SEQ ID NO: 60 , TAA+T7536C of SEQ ID NO: 61, TAA+A7589G of SEQ ID NO: 62, TAA+C8116T of SEQ ID NO: 63, TAA+C8165T of SEQ ID NO: 64,

TAA+G8281A of SEQ ID NO: 65, TAA+8386(A)n of SEQ ID NO: 66, TAA+C9000T of SEQ ID NO: 67, TAA+A9564G of SEQ ID NO: 68, TAA+G9669A of SEQ ID NO: 69, TAA+T9716A of SEQ ID NO: 70, TAA+T9839G of SEQ ID NO: 71, TAA+C9994A of SEQ ID NO: 72, TAA+C10083A of SEQ ID NO: 73, TAA+10223(A)n of SEQ ID NO: 74, TAA+A10247T of SEQ ID NO: 75, TAA+A10535G of SEQ ID NO: 76, TAA+G10704A of SEQ ID NO: 77, TAA+T10752G of SEQ ID NO: 78, TAA+C11100T of SEQ ID NO: 79, TAA+C11129A of SEQ ID NO:80, TAA+11132(CA)n of SEQ ID NO: 81, TAA+A11133G of SEQ ID NO: 82, TAA+11368del(TCTC) of SEQ ID NO: 83, TAA+T11411C of SEQ ID NO: 84, TAA+T11431C of SEQ ID NO: 85, TAA+11449ins(TTTC) of SEQ ID NO: 86, TAA+G11541A of SEQ ID NO: 87, TAA+A11602C of SEQ ID NO: 88, TAA+C11650T of SEQ ID NO: 89, TAA+C11918T of SEQ ID NO: 90, TAA+A11956C of SEQ ID NO: 91, TAA+A12143G of SEQ ID NO: 92, TAA+A12630G of SEQ ID NO: 93, TAA+T12681C of SEQ ID NO: 94, TAA+T12831C of SEQ ID NO: 95, TAA+G12834C of SEQ ID NO: 96, TAA+13236(T)n of SEQ ID NO: 97, TAA+T13971G of SEQ ID NO: 98 and TAA+G2025A of SEQ ID NO: 100, wherein said gene polymorphisms are in linkage disequilibrium with IVS3 + A6151G of SEQ ID NO: 28; the drug being at least one member selected from the group consisting of methamphetamine, methylenedioxymethamphetamine, amphetamine, dextroamphetamine, dopamine, morphine, DAMGO, codeine, methadone, carfentanil, fentanyl, heroin, cocaine, naloxone, naltrexone, nalorphine, levallorphan, pentazocine, buprenorphine, oxycodone, hydrocodone, levorphanol, etorphine, dihydroetorphine, hydromorphone, oxymorphone, ethanol, methanol, diethyl ether and tramadol.

Applicants submit that the claims, as amended, comply with the written description requirement. The polymorphisms to be used in the claimed method are specified in the amended claims. Accordingly, an ordinary artisan can envision those polymorphisms that are to be linked to individual drug sensitivity. In view of the amendment, withdrawal of the rejection is respectfully requested.

Enablement

Claims 1-8 and 14-21 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement, *see* Office Action, pages 6-12. The Examiner states that correlating polymorphisms with phenotypes is unpredictable, *see* Office Action, pages 10-11.

Claims 2-8 and 14-21 are canceled. Accordingly, the rejection is moot in regard to these claims.

As noted above, claim 1 is amended to describe linking the specified polymorphisms with drug sensitivity. As disclosed in the Ikeda Declaration, an ordinary artisan would have recognized from the present application that the specified polymorphisms in the instant claims may be linked to sensitivity to the described drugs. An ordinary artisan would have recognized from the present application that drug sensitivity can be assessed by examining the polymorphism at position IVS3-A6151G and the polymorphisms that are in linkage disequilibrium with IVS3-A6151G.

For example, Table 10 on page 59 of the present application describes that IVS3 + A6151G is associated with methamphetamine sensitivity, at a significant value of P=0.0269. Further, Table 6, as amended, describes that IVS3 + A6151G is in strong linkage disequilibrium with IVS3 + A8449G, *i.e.*, D'=1.000 and r^2=0.800. Accordingly, an ordinary artisan would have recognized that IVS3 + A8449G is also associated with drug sensitivity. This association is further supported by data obtained subsequent to the instant invention, *see* Fukuda *et al.*, *PAIN®*, 2009, *in press,* in particular Table 2 and Figure 3, (enclosed). As described in Fukuda *et al.*, IVS3 + A8449G is linked to fentanyl sensitivity. Accordingly, as stated in the Ikeda Declaration, an ordinary artisan would have recognized from the present application that IVS3+A6151G, and the polymorphisms in linkage disequilibrium with IVS3+A6151G, *e.g.*, the Table 6 polymorphisms described in the instant claims, such as IVS3+8449G, are also associated with sensitivity to the specified drugs. Accordingly, an ordinary artisan can evaluate drug sensitivity from IVS3+A6151G and the gene polymorphisms in linkage disequilibrium with IVS3+A6151G, as adequately described in the present application.

Moreover, an ordinary artisan would have recognized from the present application that the gene polymorphisms described in Table 2, as specified in the instant claims, are also in linkage disequilibrium with IVS3 + A6151G, and accordingly, are also associated with drug sensitivity. As described in Table 6 of the originally filed application, IVS3+A6151G is in strong linkage disequilibrium with TAA+A2109G and TAA+G2287A. These two polymorphisms of Table 2 are in linkage disequilibrium with the other gene polymorphisms described in Table 2 and with each other. Accordingly, an ordinary artisan would have recognized that all of the gene polymorphisms described in Table 2 are in linkage disequilibrium with IVS3+A6151G.

Based upon the foregoing, Applicants submit that the amended claims are enabled by the present application. An ordinary artisan would have recognized from the instant specification that the polymorphisms described in the claims are in linkage disequilibrium with the specified IVS3 + A6151G polymorphism, which is associated with drug sensitivity. Accordingly, all of the polymorphisms described in the claims are associated with drug sensitivity. In view of the foregoing, and the Ikeda Declaration, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendment and remarks, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact L. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: NOV 16 2009

Respectfully submitted,

By _____

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Enclosures: Electronic CRF Copy of Substitute Sequence Listing
Paper Copy of Substitute Sequence Listing
Ikeda Declaration under 37 C.F.R. § 1.132
Fukuda *et al.*